limitations from the claims ***as currently pending*** to distinguish the prior art. As no new matter or issues are thereby raised, the amendments should be entered.

Rejection Under 35 U.S.C. § 112

Claims 1-11, 16, and 20-23 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to clarify that the saliva is a sample; that the apolipoproteins in the saliva sample are being reacted with the antibodies; that the reaction is detected using a quantitative test (such as an ELISA), and the amount of apolipoproteins determined by comparison with standards of known quantities of apolipoproteins.

Claims 1, 5, 6, 7, 9, 10, and 16 have been amended using the examiner's suggested language.

Claims 20-22 have been amended to correct antecedent basis and to clarify the claimed subject matter. Claim 23 has been cancelled.

Rejections Under 35 U.S.C. § 102

Claims 1-3 and 20 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No. 5,677,133 to Oberhardt or U.S. Patent No. 5,601,911 to Oberhardt. Claims 1, 2 and 4 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No. 6,210,906 to Kundu et al. These rejections are respectfully traversed if applied to the amended claims.

Since the examiner has acknowledge that claim 12 is novel over all of the cited art, the limitations of claim 12 have been incorporated into claim 1, thereby insuring that it is novel over

Oberhardt '133, Oberhardt '991 or Kundu, et al. Claim 20 has also been amended to recite a step not shown in the prior art, comparing the amount of immunoreaction determined in step b with the amount of immunoreaction of the antibodies immunoreactive with the apolipoprotein in the saliva sample with known quantities of apolipoprotein in normal or at risk individuals. Accordingly, all claims as amended are novel over the cited art.

Rejections Under 35 U.S.C. § 103

Claims 5-7, 10-14, and 16-18 were rejected under 35 U.S.C. § 103 as obvious over Oberhardt (US 5,677,133) or Oberhardt (US 5,601,911) in view of U.S. Patent No. 5,112,758 to Fellman. Claims 7-9, 12, 14-18, and 19 were rejected as obvious over either Oberhardt in combination with Fisher, Diabetes Res. Clin. Practice 11(2) 117-119 (1991) (abstract only) and Coppo, J. Diabetic Complications 1(2), 58-60 (1987) (abstract only). Claims 21-22 were rejected as obvious over Oberhardt (US 5,677,133) or Oberhardt (US 5,601,911) in view of U.S. patent No. 6,291,178. These rejections are respectfully traversed if applied to the amended claims.

The Claimed Invention

The claimed subject matter relates to a method and an assay device or kit to detect the levels of apolipoproteins in a saliva sample that is correlated to the levels of the apolipoproteins in the serum. The advantage of such a system are readily apparent: one does not have to draw a blood sample, process it to remove the red cells, and then assay it to determine the apolipoprotein levels.

Although it was postulated that apolipoproteins were present in serum, it was not previously known that the levels could be correlated to serum levels, thereby making a non-invasive test using saliva a possibility. The Applicants demonstrated the correlation between levels of apolipoproteins in saliva and levels of HDL and LDL in serum.

The Examiner's position is that such a correlation is obvious. It is not. In fact, the dogma at the time this application was filed was that there was so much inherent variability in the saliva that although apolipoprotein was clearly present, the samples could not routinely be assayed and yield a reliable level.

In response to applicant's previous arguments on this point, the examiner has now cited U.S. patent No. 6,291,178 to Schneider. There are several aspects of Schneider however that are different. First, Schneider is a qualitative, not a quantitative, assay. This is a major difference. It is also why Schneider's system provides for extensive dilution of sample – which may alter the amount of apolipoprotein measured in a given volume, thereby completely destroying one's ability to correlate the levels of apolipoprotein measured in the sample with the levels measured in the serum. Second, Schneider's system is primarily drawn to measurements of other molecules, such as ethanol, which are known to have a correlation between saliva levels and serum levels, unlike in the present case.

This deficiency is not made up by any of the art cited by the examiner.

Oberhardt

Oberhardt (US 5,677,133), and Oberhardt (US 5,601,911) describe a method and a system of dry chemistry cascade immunoassay and affinity assay. The two Oberhardt patents

suggest that the method and system can be used in an immunoassay for with whole blood, for small molecules, large molecules including apolipoproteins, important cardiovascular proteins, cellular elements or their surface antigenic or receptor molecules, HIV antigen, hormones, signal or structural elements out side or within cells, specific polynucleotides, and diagnostic tests for difficult biological samples including saliva, etc. (See columns 3 and 4 of US 5,601,911 and US 5,677,133). Neither of the Oberhardt patents, however, specifically teaches the detection of the levels of apolipoproteins in saliva, nor, most importantly, that there is a correlation between the levels in saliva and the blood.

Neither of the Oberhardt patents provides the motivation to detect the levels of apolipoproteins in saliva. Neither of the Oberhardt patents teaches how the levels of apolipoproteins should be detected in saliva. Indeed, "saliva" is mentioned only once in the patents (Column 4, line 14 of and US 5,677,133, and Column 4, line 16 of US 5,601,911). Neither of the Oberhardt patents enables one of ordinary skill to detect the levels of apolipoproteins in saliva and extrapolate to the serum concentrations.

Kundu

Kundu describes specific antibodies to Apo A and methods to use the antibodies. Similar to the Oberhardt patents, Kundu does not teach why or how the levels of apolipoproteins should be detected in saliva, nor how to correlate the levels of the apolipoproteins in the saliva with the levels of the apolipoproteins in the serum, as defined by the amended claims.

Ullman and Kang

Ullman and Kang disclose a device for use in an immunoassay, but do not disclose a device which can be used to detect levels of apolipoprotein in saliva and correlate the levels with the levels in serum, as defined by the amended claims.

Fellman

Fellman discloses a means for reducing the viscosity of a material such as saliva which contains mucopolysaccharides, using a cationic quaternary ammonium reagent. This method could indeed be used with applicants' claimed method. However, Fellman does not suggest detecting apolipoproteins in saliva, nor that the levels could be correlated with the levels in serum.

Fisher and Coppo

Fisher and Coppo provide assays for detecting albumin – one in saliva and one in urine. Neither, however, suggest detecting apolipoproteins in saliva, nor that the levels could be correlated with the levels in serum by measuring the values of the albumin.

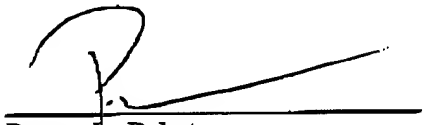
Schneider

Schneider is discussed above.

In summary, none of the prior art, alone or in combination, discloses nor makes obvious the claimed methods and kit, as defined by the amended claims.

Allowance of claims 1-22, as amended, is therefore earnestly solicited.

Respectfully submitted,



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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Patrea Pabst

Date: May 29, 2002

U.S.S.N. 08/924,994
Filed: September 5, 1998
AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims

1. (Twice Amended) A method for determining the level of an apolipoprotein in saliva comprising reacting the apolipoproteins in a saliva sample with antibodies immunoreactive with the apolipoprotein, using [in] a quantitative assay kit comprising means for collection of saliva and antibodies immunoreactive with an apolipoprotein and means for comparing the levels of the apolipoproteins in the saliva with the levels in serum, detecting the amount of immunoreactivity between the antibodies and apolipoproteins in the saliva sample as determined by the quantitative assay, and comparing the amount of determined immunoreactivity with standards of known amounts of apolipoproteins reacted with the antibodies to determine the level of apolipoproteins in the saliva sample.

2. The method of claim 1 wherein the apolipoprotein is selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof.

3. The method of claim 2 wherein the apolipoprotein is selected from the group consisting of Apo A1 and Apo B.

4. (Amended) The method of claim 1 wherein the antibodies are labelled with a detectable label.

5. (amended) The method of claim 1 [wherein] further comprising determining the level of apolipoprotein in the saliva sample [is tested] within less than three hours following collection.

6. (twice Amended) The method of claim 1 [wherein] further comprising preparing the saliva in the sample [is prepared prior to testing to remove] by removing mucopolysaccharides from the saliva prior to determining the level of apolipoprotein in the saliva sample.

AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

7. (amended) The method of claim 1 [wherein] further comprising collecting the saliva [is collected] after [stimulation] stimulating its secretion from a subject.

8. The method of claim 1 further comprising determining the amount of albumin present in the saliva.

9. (twice Amended) The method of claim 8 further comprising [normalizing] correcting the determined amount of the apoplipoprotein [to the amount] for the presence of albumin [present in the saliva of the individual from whom the saliva was obtained] in the saliva sample.

10. (amended) The method of claim 1 [wherein] further comprising collecting the saliva sample [is collected] into a device which filters out mucopolysaccharides and comprises the antibodies immunoreactive with one or more of the apolipoproteins in the saliva sample.

11. The method of claim 10 wherein the apolipoprotein is either Apo A1 or Apo B.

12. An assay device or kit for determining the amount of apolipoprotein in a saliva sample comprising means for collection of saliva and antibodies immunoreactive with an apolipoprotein for use in a quantitative assay, and means for comparing the levels of the apolipoproteins in the saliva with the levels in serum.

13. (amended) The assay device or kit of claim 12 comprising filter means for removal of mucopolysaccharides from the saliva.

14. The assay device or kit of claim 12 wherein the antibodies are reactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof.

AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

15. The assay device or kit of claim 12 further comprising antibodies immunoreactive with albumin.

16. (twice Amended) The assay device or kit of claim 12 wherein the antibodies immunoreactive with apolipoprotein in the saliva sample are immobilized on a solid support.

17. The assay device or kit of claim 16 comprising reagents for detection of complexes between the apolipoprotein and the antibodies.

18. (Amended) The assay device or kit of claim 12 comprising a strip or dipstick.

19. (Amended) The assay device or kit of claim 15 comprising as separate reagents antibodies to [an] the apolipoprotein and antibodies to albumin.

20. (twice Amended) A method for quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease comprising

(a) reacting the apolipoproteins in a saliva sample with antibodies specifically immunoreactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof in a quantitative assay,

(b) determining the amount of immunoreaction between the antibodies and the apolipoproteins in the saliva sample, and

(c) comparing the amount of immunoreaction determined in step b with the amount of immunoreaction of the antibodies immunoreactive with the apolipoprotein in the saliva sample with known quantities of apolipoprotein in normal or at risk individuals.

21. (amended) The method of claim 1 further comprising,

[determining the correlation between] correlating the levels of HDL and/or LDL in the serum with [and] the levels of [apoprolipoproteins] apolipoproteins in serum, [and]

[determining] correlating the levels of the apolipoproteins in the serum based on the levels of apolipoproteins determined in the saliva sample, and

extrapolating the levels of HDL and/or LDL in the serum, based on the [measurements of the] levels of the apolipoproteins determined in the saliva sample.

22. (amended) The method of claim 20 comprising [quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease by] reacting [a] the apolipoprotein in the saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof, and

correlating the levels of at least one apolipoprotein in the saliva with the levels of apolipoprotein in serum known to be correlated to [associated with] the presence of lipid disorders or risk of cardiovascular disease.

Please cancel claim 23.